DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our Reference No.: 98-0012

August 24, 1998

Mr. Martin Page
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355

Dear Mr. Page:

Your biologics license application for Infliximab is approved effective this date. Centocor, Inc., Malvern, Pennsylvania, is hereby authorized to manufacture and ship for sale, barter, or exchange in interstate and foreign commerce Infliximab under Department of Health and Human Services Biologics License No. 1242.

Infliximab is indicated for the treatment of moderately to severely active Crohn's disease for the reduction of the signs and symptoms, in patients who have an inadequate response to conventional therapies; and treatment of patients with fistulizing Crohn's disease for the reduction in the number of draining enterocutaneous fistula(s).

Under this authorization, you are approved to manufacture Infliximab at your facility in Leiden, The Netherlands. Final formulated drug product will be filled, lyophilized, labeled, and packaged at (———————————) and distributed from (———————————): (———————————). In accordance with approved labeling, your product will bear the tradename Remicade, and will be marketed in single use vials containing 100 mg of Infliximab.

You are not currently required to submit samples of future lots of Infliximab to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

The dating period for Infliximab shall be 18 months from the date of manufacture when stored at 2 - 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the final formulated product. The drug substance may be stored for up to 12 months at -40°C. Results of ongoing stability studies should be submitted throughout the dating period as they become available including the results of stability studies from the first three production lots.

Any changes in the manufacture, packaging or labeling of the product or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

As requested in your letter of June 22, 1998, marketing approval of this product is granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as a basis for approvals of products intended for serious or life-threatening illnesses or conditions.

Approval of Infliximab under these regulations requires, among other things, that you study the biological product further to address the uncertainty as to the relationship of observed clinical benefit to outcomes following continued use beyond the approved regimen and that such studies be carried out with due diligence. As stated in 21 CFR 601.43 and clarified in our letter dated August 13, 1998, if you fail to meet these requirements the Agency may, following a hearing, withdraw or modify approval.

Granting of this approval requires completion of a randomized, double-blind, placebo-controlled clinical study(s), as outlined in your commitment of July 31, designed to evaluate safety and efficacy of continued use of Infliximab for maintaining a sustained clinical outcome in patients with moderately to severely active Crohn's disease, including patients with draining enterocutaneous fistula(s).

Design, initiation, accrual, completion, and reporting of these studies is expected to occur within the framework described in your letter of August 13, 1998. It is understood that, to fulfill the requirements of accelerated approval, the study(s) must be appropriately designed and conducted with due diligence to evaluate the clinical benefit of continued treatment with Infliximab beyond the approved regimen.

In addition, we acknowledge the following post-approval commitments which are fully described in your letters of May 26, June 11, June 30, July 13, July 23, July 24, July 27, July 31, and August 4, 1998, which include the following:

1. To conduct a clinical trial in pediatric patients with Crohn's disease in order to determine consistency of benefits with those observed in adults.

2. To submit infusion reaction rate data by product lot for the rheumatoid arthritis clinical trial by December 31, 1998 and for the Phase IV clinical trial in Crohn's disease when available.

3. To submit a release specification and an alert limit for ——— IgG after ten, 8 kg scale lots of Infliximab drug substance have been manufactured. In the interim, no material will be released with ———IgG levels greater than ——— without prior consultation with CBER.

4. To submit the protocol and results for the cleaning validation of the ——— chromatography column control unit by October, 30 1998.

5. To submit the protocol and final study report for an additional study characterizing host cell proteins in the drug substance by December 3, 1998. Based upon data in this report, an upper limit specification will be established.

6. To submit the results of hold period studies for in-process product intermediates that include a container-closure integrity study by October 15, 1998, and biochemical, bioburden and endotoxin studies on a periodic basis.

7. To submit revised yield specifications from stages 4 through 9 of the drug substance manufacturing process after 10 additional lots of purified frozen bulk are manufactured.

8. To submit for review and approval the initial core promotional items and all other promotional materials to be used within the first 120 days following today's date.

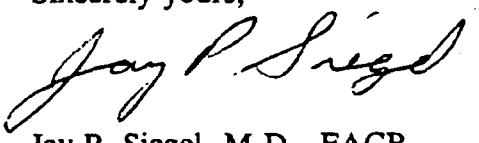
9. We also acknowledge additional information in your letters of May 26, June 11, July 23 and August 4, 1998 addressing the agency's observations noted during the April 20 - May 1, 1998 inspection and your commitments to submit additional information and data within the timelines specified.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form (FDA Form 2567) with completed implementation information. In addition, as specified in 21 CFR 601.45, any advertising and promotional labeling is required to be submitted for review and approval using FDA Form 2567 to the Advertising and Promotional Labeling Staff, Center for Biologics Evaluation and Research, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448 at least 30 days prior to the initial publication of any advertisement or to the initial dissemination of any promotional labeling.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,



Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research